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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,381	09/25/2001	Gary Lynch	1819.0040001/MAC/LBB	7154

26111 7590 08/19/2005

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EXAMINER	
DOWELL, PAUL THOMAS	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,381	LYNCH ET AL.	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12,14-19, 36, 37; 59, 61-68 and 70-75* is/are pending in the application.

4a) Of the above claim(s) *9-12 and 65-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,14-19,36,37,59,61-64 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after final rejection and after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 06/08/2005 has been entered.

The amendment filed 06/08/2005 canceling Claims 20-35, 38-54, 55-58 and 76-79, withdrawing Claims 9-12 and 65-68 and ammending Claims 1 and 59 has been entered. The amendment filed 06/08/2005 returning the language of the specification to that as found in the application as filed and cancellation of Claim 79 overcomes the new matter rejection under 35 U.S.C. § 132 made by the Examiner in the 9/8/04 office action.

Claims 1, 3-8, 14-19, 36-37, 59, 61-64, 70-75, drawn to an *in vitro* method for determining the effect of a substance on sequestration, uptake or accumulation of amyloid deposition in brain cells, are under examination in the instant office action.

Priority

Applicant's claim to priority of Provisional Application 60/235,374 (09/25/200) is acknowledged.

Claim Objections

Claims 14 and 15 are objected to because they depend from a canceled claim (i.e. claim 13). Appropriate correction is required. It is noted that claims 14 and 15 are interpreted to depend from claim 1.

Claims 63 is objected to because it depends from a canceled claim (i.e. claim 60). Appropriate correction is required. It is noted that claim 63 is interpreted to depend from claim 59.

Claims 70 and 71 are objected to because they depend from a canceled claim (i.e. claim 69). Appropriate correction is required. It is noted that claims 70 and 71 are interpreted to depend from claim 59.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description

Claims 1 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain

subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is drawn to a method for determining the effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells, said method comprising exposing brain cells to an integrin antagonist, wherein said antagonist is not TGFβ.

When Claims 1 and 59 are analyzed in light of the specification, said method encompasses exposing brain cells to any integrin antagonist wherein said antagonist is not TGFβ and as such would encompass a large number of molecules that have divergent structure and function. However, the specification on page 19 discloses only neutralizing or function blocking anti-integrin antibodies (alpha1 through alpha8, beta1 through beta8), RGD peptides that are integrin antagonists (RGDS, GRGDS, GRGDSP, GRGDTP, mimetics therof and disintegrins such as echistatin), amyloid beta peptide, oxidative free radicals ($OH^{\cdot}$, $O_2^{\cdot}$), lysosomal enzyme inhibitors (chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenyl-alanine-diazomethylketone, β-amyloid and mimetics thereof) and inflammatory factors (TGFβ, IL-1β, LPS) as a list of integrin antagonists.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the RGD peptide integrin antagonists RGDS, GRGDS, GRGDSP and GRGDTP are the only

species of integrin antagonists whose complete structure is disclosed. While the specification describes the structure of the RGD peptides RGDS, GRGDS, GRGDSP and GRGDTP and lists other antagonists, no core structure for an integrin antagonist has been disclosed. The other antagonists listed (e.g. anti-integrin antibodies, oxidative free radicals, inflammatory factors, for example) do not share any common structure. The specification does not provide any disclosure as to what would have been the complete structure of a sufficient number of species of the claimed genus that would have been representative of the entire genus of integrin antagonists.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than amino acid sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only identifying characteristic of integrin antagonists is that they modulate integrins and/or integrin receptors or that they are integrin antagonists. Such limitations cannot be identifying characteristics for the claimed diverse genus of molecules because all members of the claimed genus will have those functional characteristics.

The invention of Claims 3-8, 14-19, 36, 37 require the invention of Claim 1 and the invention of Claims 61-64, 70-75 require the invention of Claim 59 and therefore are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons described above.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Further, Applicant's attention is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In summary the specification does not describe the complete structure of a representative number of species of the large genus of integrin antagonists. Further, the specification does not sufficiently describe a representative number of species of the large genus of integrin antagonists by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant was in possession of the genus at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

Enablement

Claims 1 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the

effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells, said method comprising:

(A) exposing brain cells to an integrin antagonist, wherein said antagonist is selected from the group consisting of function blocking anti-α5 subunit integrin antibody, function blocking anti-β1 subunit integrin antibody, RGDS peptide, GRGDS peptide, GRGDSP peptide, GRGDTP peptide, echistatin and β-amyloid;

(B) maintaining said cells for a time sufficient to induce sequestration, uptake or accumulation of amyloid in said cells as a result of said antagonist;

(C) adding said substance before, during and/or after said exposing or maintaining; and

(D) determining whether the presence of said substance has an effect on said antagonist induced sequestration, uptake or accumulation of amyloid,

does not reasonably provide enablement for a method of determining the effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells, said method comprising:

(A) exposing brain cells to any integrin antagonist, wherein said antagonist is is not TGFβ;

(B) maintaining said cells for a time sufficient to induce sequestration, uptake or accumulation of amyloid in said cells as a result of said antagonist;

(C) adding said substance before, during and/or after said exposing or maintaining; and

(D) determining whether the presence of said substance has an effect on said antagonist induced sequestration, uptake or accumulation of amyloid.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is drawn to a method for determining the effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells, said method comprising exposing brain cells to an integrin antagonist, wherein said antagonist is not TGFβ. Reasonably interpreted, the claimed invention reads broadly on said method comprising exposing brain cells to any integrin antagonist, wherein said antagonist is not TGFβ.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, the USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in

the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The specification discloses a general laundry list of integrin antagonists including: neutralizing or function blocking anti-integrin antibodies that interact with integrin subunits alpha1-alpha8 and beta1-beta8, RGD peptides that are integrin antagonists (RGDS, GRGDS, GRGDSP, GRGDTP, mimetics therof and disintegrins such as echistatin), amyloid beta peptide, oxidative free radicals ($OH^{\cdot}$, $O_2^{\cdot}$), lysosomal enzyme inhibitors (chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenyl-alanine-diazomethylketone, β-amyloid and mimetics thereof) and inflammatory factors (TGFβ, IL-1β, LPS) (page 19, parags. 0064-0065). The specification recites that other integrin antagonists and/or agents which modulate integrins and/or integrin receptors are readily determinable by those skilled in the art (page 37, parag. 0120). Working example 1 demonstrates increased uptake of β-amyloid in brain slices incubated in the presence of either the RGD peptide, GRGDSP, or the disintegrin, echistatin, compared to control brain slices incubated with only β-amyloid (page 50, Table I).

However, the specification as filed does not provide sufficient guidance to practice the claimed method with <u>any</u> integrin antagonist and an artisan of skill would have required extensive experimentation to practice the claimed invention commensurate with the scope of the claims. Such experimentation will be undue

because of the unpredictability of practicing the claimed method using any integrin antagonist. The specification does not provide sufficient guidance to address these issues for an artisan to practice the claimed invention.

Regarding practice of the claimed invention with anti-integrin antibodies as integrin antagonists. The specification (page 3, paragr. 0009, lines 12-17) and the art of record at the time of the invention teach only $\alpha 5\beta 1$ integrin (Matter et al, The Journal of Cell Biology, 141:1019-1030, 1998) as the integrin mediator of β-amyloid deposition in cells. Further, the art of record at the time of the invention recognized only $\beta 1$–containing integrins as interacting with β-amyloid (Ghiso et al, Biochemical Journal, 288:1053-1059, 1992; Sabo et al, Neuroscience Letters, 184:25-28, 1995). Thus, an artisan would reasonably accept that said method could be practiced with function blocking anti-$\alpha 5$ and anti-$\beta 1$ subunit integrin antibodies. However, the specification provides no specific guidance or working examples as to how an artisan would practice the claimed method using function blocking anti-integrin antibodies to any integrin subunits. At the time of the invention, it was known that there was a large number of integrin receptors that mediate a diverse set of biological functions (Huang et al, Cellular and Molecular Life Sciences, 54:527-540, 1998; page 528, col. 1, lines 2-7). Therefore, an artisan would experience undue experimentation to practice the claimed invention with any function blocking anti-integrin antibody because an artisan would not know how to choose any function blocking anti-integrin antibody that would be operative in the claimed invention with any degree of predictability.

Regarding practice of the claimed invention with RGD peptides as integrin antagonists. The specification discloses Working example 1 which demonstrates increased uptake of β-amyloid in brain slices incubated in the presence of the RGD peptide, GRGDSP, compared to control brain slices incubated with only β-amyloid (page 50, Table I). The art of record at the time of the invention recognized RGD peptides as pan-integrin antagonists and an artisan of skill could use RGDS, GRGDS, GRGDSP or GRGDTP to practice the claimed invention with a reasonable degree of predictability. For example, Huang et al (Huang et al, Cellular and Molecular Life Sciences, 54:527-540, 1998) teaches that RGD peptides effectively inhibited binding of multiple ligands to αIIβ3, αvβ3 and α5β1 integrins (page 531, col. 2, parag. 1, lines 10-15) suggesting that RGD peptides are general pan-integrin antagonists. Therefore, the specification in light of the art of record at the time of the invention is enabling as to how an artisan would practice the claimed method using the RGD peptides RGDS, GRGDS, GRGDSP and GRGDTP.

Regarding practice of the claimed invention with disintegrins as integrin antagonists. The specification discloses Working example 1 which demonstrates increased uptake of β-amyloid in brain slices incubated in the presence of the disintegrin, echistatin, compared to control brain slices incubated with only β-amyloid (page 50, Table I). However, Scarborough et al (Journal of Biological Chemistry, 266:9359-9362, 1991) teach that the disintegrins "barbourin, tergeminin and eristicophin weakly inhibited the binding of fibronectin to α5β1 compared with the disintegrin echistatin" (page 9360, col. 2, lines 9-11, also see

Table I) demonstrating that the art of record at the time of the invention recognized that distintegrins exhibit divergent specificity and distinct antagonistic properties for different integrins, in particular $\alpha 5\beta 1$ integrin. Because the specification and the art of record at the time of the invention teach only $\alpha 5\beta 1$ integrin as the integrin mediator of β-amyloid deposition in cells (as previously discussed), an artisan would be skeptical that barbourin, tergeminin and eristocophin, for example, would be operative in the claimed invention as disclosed for echistatin in Working example 1. Thus, the specification in light of the art of record at the time of the invention is enabling as to how an artisan would practice the claimed method with echistatin as the integrin antagonist. However, the specification does not provide specific guidance or working examples, and therefore is not enabling, as to how an artisan would practice the claimed method with any disintegrin as the integrin antagonist.

Regarding practice of the claimed invention with β-amyloid as the integrin antagonist. The specification discloses Working example 1 which demonstrates uptake of β-amyloid in brain slices incubated with β-amyloid alone (page 50, Table I). As discussed in more detail in the art rejections, both the specification and the art of record at the time of the invention teach that β-amyloid is an integrin antagonist. Therefore, an artisan of skill could use β-amyloid to practice the claimed invention with a reasonable degree of predictability and the specification is enabling as to how an artisan would practice the claimed method with β-amyloid as an integrin antagoinist.

Regarding practice of the claimed invention with oxidative free radicals, lysosomal enzyme inhibitors and inflammatory factors as integrin antagonists. The specification is silent with respect to oxidative free radicals, lysosomal enzyme inhibitors and inflammatory factors as integrin antagonists. No specific guidance or working examples are disclosed in the specification as to how an arstian would practice the claimed invention with oxidative free radicals, lysosomal enzyme inhibitors or inflammatory factors as integrin antagonists. Therefore, an artisan would experience undue experimentation because an artisan would not know how to choose oxidative free radicals, lysosomal enzyme inhibitors or inflammatory factors as integrin antagonists that would be operative in the claimed invention with any degree of predictability.

In light of the lack of specific guidance and working examples from the specification, an artisan of skill would have required extensive experimentation to practice the claimed invention with any integrin antagonist, such experimentation would have been undue because of the lack of predictability.

Therefore, limiting the scope of the claimed invention to a method of determining the effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells, said method comprising:

(A) exposing brain cells to an integrin antagonist, wherein said antagonist is selected from the group consisting of function blocking anti-α5 subunit integrin antibody, function blocking anti-β1 subunit integrin antibody, RGDS peptide, GRGDS peptide, GRGDSP peptide, GRGDTP peptide, echistatin and β-amyloid;

(B) maintaining said cells for a time sufficient to induce sequestration, uptake or accumulation of amyloid in said cells as a result of said antagonist;

(C) adding said substance before, during and/or after said exposing or maintaining; and

(D) determining whether the presence of said substance has an effect on said antagonist induced sequestration, uptake or accumulation of amyloid, is proper.

The invention of Claims 3-8, 14-19, 36, 37 require the invention of Claim 1 and the invention of Claims 61-64, 72-75 require the invention of Claim 59 and therefore are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons described above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4, 7, 8, 16-18, 37, 59, 63, 64, 72-74 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995).

It is noted to Applicant that, in the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention.

Harris-White teaches hippocampal slices as an *in vitro* model for amyloid-β deposition (page 10368, col. 1, parag. 1, lines 1-3). Specifically, Harris-White teaches a method for determining the effect of TGFβ on amyloid-β deposition using the hippocampal slice model where the hippocampal slice is incubated simultaneously in media comprising both TGFβ and amyloid-β (page 10368, col. 2, first paragraph). Harris-White teaches that treatment of hippocampal slices with amyloid-β alone resulted in significant amyloid-β deposition compared to untreated controls (page 10368, col. 2, parag. 4, lines 3-5). Harris-White further teaches that TGFβ, when added to hippocampal slice cultures with amyloid-β, results in a 2 to 3-fold increase in the amount of amyloid-β within the slice compared to controls treated with amyloid-β alone (page 10368, col. 2, parag. 4, lines 5-7). Harris-White teaches detection of the increase in amyloid-β deposition in hippocampal brain slices with antibodies to regions of the amyloid-β polypeptide by both visual imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5).

It is noted that it was known in the art of record at the time of the invention that amyloid-β peptide binds to integrins and that amyloid-β peptide functions as an integrin antagonist. For example, Sabo et al teaches that amyloid-β inhibits adhesion of a neuroblastoma cell line to fibronectin (see Figure 2). Sabo et al further recite:

> The ability of β/A4 to inhibit adhesion to fibronectin, albeit partially, was consistent with its association with integrin (page 27, col. 2, parag. 1, lines 1-3).
>
> Interactions of β/A4 peptides with integrins could have both physiological and pathogenic implications. During development, for example, intergrin-mediated adhesion, which appears relevant to neuronal migration and axon outgrowth, could be modulated by secreted β/A4, as shown here (page 28, col. 1, parag. 2, lines 1-6).
>
> Pathogenically, it is possible that β/A4 peptides, which accumulate in Alzheimer's-afflicted brain tissue in the form of aggregates, could disrupt normal integrin function (page 28, col. 1, parag. 2, lines 11-14).

Since integrins function as adhesion molecules, amyloid-β binds integrins and amyloid-β antagonizes integrin-mediated adhesion as taught by Sabo et al, it would have been clear to an artisan of ordinary skill at the time of the invention that amyloid-β can function as an integrin antagonist.

Therefore, Harris-White clearly anticipates the claimed invention.

Response to Arguments

Applicant's arguments filed 06/08/2005 have been fully considered, but are not persuasive. In the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention. Amending Claims 1 and 59 to recite, "wherein said antagonist is not TGFβ " does not overcome the rejection because amyloid-β is the integrin antagonist that is not TGFβ.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 6, 36, 59, 61, 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) in view of Matter et al (The Journal of Cell Biology, 141:1019-1030, 1998).

It is noted to Applicant that, in the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention.

It is further noted to Applicant that, in the method taught by Matter et al, DNA sequences encoding integrin α5 are considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention.

Harris-White teaches hippocampal slices as an *in vitro* model for amyloid-β deposition (page 10368, col. 1, parag. 1, lines 1-3). Specifically, Harris-White teaches a method for determining the effect of TGFβ on amyloid-β deposition using the hippocampal slice model where the hippocampal slice is incubated simultaneously in media comprising both TGFβ and amyloid-β (page 10368, col. 2, first paragraph). Harris-White teaches that treatment of hippocampal slices with amyloid-β alone resulted in significant amyloid-β deposition compared to untreated controls (page 10368, col. 2, parag. 4, lines 3-5). Harris-White further teaches that TGFβ, when added to hippocampal slice cultures with amyloid-β, results in a 2 to 3-fold increase in the amount of amyloid-β within the slice compared to controls treated with amyloid-β alone (page 10368, col. 2, parag. 4, lines 5-7). Harris-White teaches detection of the increase in amyloid-β deposition in hippocampal brain slices with antibodies to regions of the amyloid-β polypeptide by both visual imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5).

Harris White does not teach a decrease in amyloid-β deposition and Harris-White does not teach adding a substance prior to exposing to an integrin antagonist.

Matter teaches that integrin α5-negative neuroblastoma cells, IMR-324β1, transfected with DNA sequences encoding integrin α5 prior to exposing the cells to amyloid-β, results in a 5-fold decrease in accumulation of amyloid-β deposition in the cells as compared to non-transfected control cultures (page 1024, col. 1, parag. 1, lines 4-6).

Matter does not teach a method using brain slices.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the hippocampal brain slice method of Harris-White by adding a substance prior to exposure to an integrin antagonist (i.e. amyloid-β) and to use the modified method to determine whether said substance is capable of inhibiting amyloid-β deposition as taught by Matter with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to use the hippocampal brain slice assay of Harris-White because the brain slice assay is more reflective of the *in vivo* situation as recognized by Harris-White (page 10368, col. 1, parag. 1, lines 2-10).

Response to Arguments

Applicant's arguments filed 06/08/2005 have been fully considered, but are not persuasive. In the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention. It is further noted that in the method taught by Matter et al, DNA sequences encoding integrin α5 are considered to be the "substance" and amyloid-β is considered to be the

"integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention. Amending Claims 1 and 59 to recite, "wherein said antagonist is not TGFβ" does not overcome the rejection because amyloid-β is the integrin antagonist that is not TGFβ in the methods taught by both Harris-White and by Matter.

Applicant's argue that Matter does not cure the deficiencies of Harris-White. Matter teaches adding a substance (i.e. DNA sequences encoding integrin α5) prior to exposure to an integrin antagonist (i.e. amyloid-β) and to use the modified method to determine whether said substance is capable of inhibiting amyloid-β deposition.

Claims 1, 14, 15, 59, 70, 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) in view of Matter et al (The Journal of Cell Biology, 141:1019-1030, 1998).

It is noted to Applicant that, in the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention.

It is further noted to Applicant that, in the method taught by Matter et al, DNA sequences encoding integrin α5 are considered to be the "substance" and amyloid-β, anti-integrin α5 antibody and GRGDSP peptides are considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention.

Harris-White teaches hippocampal slices as an *in vitro* model for amyloid-β deposition (page 10368, col. 1, parag. 1, lines 1-3). Specifically, Harris-White teaches a method for determining the effect of TGFβ on amyloid-β deposition using the hippocampal slice model where the hippocampal slice is incubated simultaneously in media comprising both TGFβ and amyloid-β (page 10368, col. 2, first paragraph). Harris-White teaches that treatment of hippocampal slices with amyloid-β alone resulted in significant amyloid-β deposition compared to untreated controls (page 10368, col. 2, parag. 4, lines 3-5). Harris-White further teaches that TGFβ, when added to hippocampal slice cultures with amyloid-β, results in a 2 to 3-fold increase in the amount of amyloid-β within the slice compared to controls treated with amyloid-β alone (page 10368, col. 2, parag. 4, lines 5-7). Harris-White teaches detection of the increase in amyloid-β deposition in hippocampal brain slices with antibodies to regions of the amyloid-β polypeptide by both visual imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5).

Harris-White does not teach integrin antagonists other than amyloid-β.

Matter teaches that integrin α5-negative neuroblastoma cells, IMR-324β1, transfected with DNA sequences encoding integrin α5, when incubated with amyloid-β, results in a 5-fold decrease in amyloid-β deposition in the cells as compared to non-transfected control cultures (page 1024, col. 1, parag. 1, lines 4-6). Matter teaches that amyloid-β deposition returned to control levels in the presence of an anti-integrin α5 antibody (page 1024, col. 1, parag. 1, lines 4-9).

Matter further teaches that GRGDSP peptide inhibits amyloid-β binding to the cells (page 1023, col. 1, parag. 1, lines 23-33).

Matter does not teach a method using brain slices.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the hippocampal brain slice method of Harris-White by using anti-integrin antibodies and/or GRGDSP peptide as integrin antagonists as taught by Matter with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to use the hippocampal brain slice assay of Harris-White because the brain slice assay is more reflective of the *in vivo* situation as recognized by Harris-White (page 10368, col. 1, parag. 1, lines 2-10).

Response to Arguments

Applicant's arguments filed 06/08/2005 have been fully considered, but are not persuasive. In the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention. It is further noted that in the method taught by Matter et al, DNA sequences encoding integrin α5 are considered to be the "substance" and amyloid-β, anti-integrin α5 antibody and GRGDSP peptides are considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention. Amending Claims 1 and 59 to recite, "wherein said antagonist is not TGFβ" does not overcome the rejection because amyloid-β, anti-integrin α5 antibody and GRGDSP peptides are the

integrin antagonists that are not TGFβ in the methods taught by both Harris-White and by Matter.

Applicant's argue that Matter does not cure the deficiencies of Harris-White. Matter teaches anti-integrin antibodies and GRGDSP peptide as integrin antagonists.

Claims 1, 19, 59, 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) in view of Hass et al (The Journal of Biological Chemistry, 273:13892-13897, 1998).

It is noted to Applicant that, in the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention.

Harris-White teaches hippocampal slices as an *in vitro* model for amyloid-β deposition (page 10368, col. 1, parag. 1, lines 1-3). Specifically, Harris-White teaches a method for determining the effect of TGFβ on amyloid-β deposition using the hippocampal slice model where the hippocampal slice is incubated simultaneously in media comprising both TGFβ and amyloid-β (page 10368, col. 2, first paragraph). Harris-White teaches that treatment of hippocampal slices with amyloid-β alone resulted in significant amyloid-β deposition compared to untreated controls (page 10368, col. 2, parag. 4, lines 3-5). Harris-White further teaches that TGFβ, when added to hippocampal slice cultures with amyloid-β,

results in a 2 to 3-fold increase in the amount of amyloid-β within the slice compared to controls treated with amyloid-β alone (page 10368, col. 2, parag. 4, lines 5-7). Harris-White teaches detection of the increase in amyloid-β deposition in hippocampal brain slices with antibodies to regions of the amyloid-β polypeptide by both visual imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5).

Harris-White does not teach apoE deficient or apoE4 containing brain cells.

Hass et al teaches protein-protein interactions between the amyloid-β precursor protein APP and apoE2, apoE3 & apoE4 (page 13896, col. 1, parag. 1, lines 7-9). Hass et al also recognizes that the apoE4 isoform is associated with development of Alzheimer's disease (page 13892, col. 1, parag. 1, lines 10-12) and that apoE4 is considered a susceptibility factor for Alzheimer's disease (page 13892, col. 2, line 4).

Hass does not teach a method using brain slices.

It would have been obvious to an artisan of ordinary skill at the time of the invention to modify the hippocampal brain slice method of Harris-White by substituting brain slices containing cells that are apoE deficient or apoE4 expressing with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to examine the effect of apoE deficiency or apoE4 overexpression on amyloid-β deposition because of the known protein-protein interaction between apoE and amyloid-β and because of the known genetic link between apoE and Alzheimer's disease as taught by Hass et al; and to use the

hippocampal brain slice assay of Harris-White because the brain slice assay is more reflective of the *in vivo* situation as recognized by Harris-White (page 10368, col. 1, parag. 1, lines 2-10).

Response to Arguments

Applicant's arguments filed 06/08/2005 have been fully considered, but are not persuasive. In the method taught by Harris-White, TGFβ is considered to be the "substance" and amyloid-β is considered to be the "integrin antagonist, wherein said antagonist is not TGFβ" of the claimed invention. Amending Claims 1 and 59 to recite, "wherein said antagonist is not TGFβ " does not overcome the rejection because amyloid-β is the integrin antagonist that is not TGFβ in the method taught by Harris-White.

Applicant's argue that Hass does not cure the deficiencies of Harris-White. Hass teaches a protein-protein interaction between apoE and amyloid-β and recognizes the genetic link between apoE and Alzheimer's disease

Conclusions.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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